

REMARKS

Applicant respectfully requests entry of the amendments and consideration of the remarks submitted herein.

INTERVIEW SUMMARY

A telephonic interview of this application was conducted between Examiner Orwig and Applicant's representative, Paul Saveriede. The combination of Uhrich and Tian under 35 U.S.C. §103(a) was discussed. Applicant's representative pointed to differences in the molecules disclosed in each reference. The Examiner asserted that both references disclose complexes having hydrophobic cores that would motivate the person of ordinary skill to combine the references. No agreement was reached.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1-2, 8-23, 240 and 241 under 35 USC §103(a) as being unpatentable over Tian (Tian et al., "Polymer Preprints" (2002) 43(2); 719-720) in view of Uhrich (WO 03/005959).

This rejection is respectfully traversed. As noted previously, the Supreme Court set out the analysis for patentability under 35 USC 103(a): the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined (see, e.g., *Graham v. John Deere Co.*, 383 U.S. 1 (1966) and *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007)).

The Examiner states that Applicants' arguments have been fully considered but are not persuasive. The Examiner has set forth the maintained rejection in the Final Office Action. In the Response to Arguments section beginning on page 7, the Examiner states:

"Applicants' arguments have been fully considered but are not persuasive.

Applicants assert that they have not argued the references individually, stating "Indeed, the Applicants have specifically argued that Uhrich does not provide the teaching and suggestion the use of the compounds claimed in present application for the removal of LDL and/or the treatment of atherosclerosis and, in conjunction with the Examiner's concession that Tian does not disclose the use of the disclosed compounds for

LDL removal or treatment of atherosclerosis, the rejection should be withdrawn" (response, p.6-7).

However, this argument, like those put forth previously, amounts to a statement of the deficiencies of the individual references and fails to appreciate the combined teachings of the references, and what they suggest to one of skill in the art. As detailed in the prior Office Action, and reiterated above, the combination of Tian and Uhrich renders the claims obvious for the reasons of record."

Applicants disagree. Applicants assert that the deficiencies in the references are such that no combination of their disclosures is sufficient sustain the rejection. Applicants have pointed out the deficiencies in the disclosures of each of Tian and Uhrich *and* have pointed to several key differences between the disclosures of Tian and Uhrich:

- 1) The macromolecules of Tian are aggregates that self assemble in solution;
- 2) The macromolecules of Uhrich are unimolecular;
- 3) The macromolecules of Uhrich do not aggregate;
- 4) The macromolecules of Uhrich each contain a molecular core that is a polyol or polyacid;
- 5) There is no disclosure in Tian of a polyol or polyacid moiety connecting the molecules of Tian; and
- 6) The polyol or polyacid core of Uhrich provides a thermodynamic stability over the molecules of Tian.

One of the critical differences between Tian and Uhrich is that the molecules of Tian *aggregate* to form micelles, while the molecules of Uhrich *are* micelles: unimolecular micelles.

It appears from the characterization of these references by the Examiner, that there is no appreciation of this difference. In Paragraph 4 of the Claim Rejections - 35 USC § 103 (Maintained) section of the Office Action, the Examiner admits that the molecules of Tian are "part of the structure" of the macromolecules disclosed by Uhrich. The Examiner further admits that Tian's molecules are "intermediates" in forming the ASMs of Uhrich.

However, in Paragraph 5 of this section of the Office Action, the Examiner begins with the premise "Given the similarity of the micelles formed by each of these molecules, ...". The Examiner also alleged that the "micelles" of Tian and Uhrich are "similar". However, no explanation was given for why the aggregates of Tian and the ASMs of Uhrich are "similar",

other than the assertion that the molecules of Tian can be used in the synthesis of the ASMs of Uhrich. Neither does the Examiner explain why this alleged similarity would provide one of ordinary skill a reasonable expectation of success in applying the disclosure of Uhrich to the disclosure of Tian to use Tian's molecule in accordance with the claimed invention.

Therefore, the disclosures of Tian and Uhrich, alone or together, remain insufficient to render the pending claims obvious.

The Examiner continues:

“Applicants discount the need for evidence to rebut the prima facie case of obviousness that has been established. Applicants instead assert that because the molecules of Tian are linked by a (small) core molecule in Uhrich, an artisan would appreciate that the linkage would change the conformation and behavior in solution of the Tian molecules (response, p. 7).

This argument continues to ignore the fact that both Tian and Uhrich teach that the molecules, both the intermediate "monomers" of Tian and the covalently linked "polymeric" forms of Uhrich, are taught to function in *precisely the same way*, forming stable micelles in solution that have a hydrophobic core and act as microcontainers for lipophilic compounds. Thus, the express teachings of Tian and Uhrich directly refute applicants' assertion. Since Tian directly teaches that the non-polymerized molecules form micelles capable of transporting lipophilic compounds (just like those of Uhrich), a skilled artisan would understand that it is the amphiphilic portions (i.e. Tian's molecules) themselves that are responsible for the sequestration of the hydrophobic compounds (i.e. per Tian's Scheme 1) rather than a small polyfunctional core that is present merely to link several of the amphiphilic compounds together. One would clearly have a reasonable expectation of success in using Tian's molecules for the same purposes as those described for the polymerized versions of Uhrich.” [emphasis by the Examiner]

It is precisely the emphasized portion of the section that highlights the deficiency in the combination of these references. That is, there is no disclosure that the molecules operate the same way. Tian discloses that the two polymers disclosed in the reference *aggregate* to form “20 nm stable aggregates”. No data in regard to these aggregates is given beyond the size of the aggregates is given. No disclosure of encapsulation of any agents, including lipoproteins, is present in Tian.

In Uhrich, however, the disclosure specifically states that the ASM molecules do not aggregate. Uhrich describes the micelles disclosed therein as “unimolecular” micelles (see e.g. Uhrich at page 34, line 13). Uhrich goes on to state that: “Unlike conventional micelles, however, the polymeric micelles of the present invention are thermodynamically stable because of the covalent linkages between the polymer arms. The ability to encapsulate small molecules,

the enhanced solubility and the *lack of aggregation* characterize the usefulness of these polymers as drug delivery systems.” (Uhrich, page 34, lines 23-27)(emphasis added). Therefore, the molecules of Uhrich do not function “in precisely the same way” as the molecules of Tian because the molecules of Uhrich *do not* form aggregates.

Because of the differences in structure and the formation of the molecules of Tian and of Uhrich, the person of ordinary skill would not have been motivated to combine the disclosures of these references nor would they have had a “reasonable” expectation of success in using the molecules of Tian to arrive at the claimed invention.

The Examiner continues:

“Applicants refer to Uhrich at p. 34, lines 21-22, asserting that Uhrich teaches that it is the core that forms the hydrophobic microenvironment that encapsulates small hydrophobic molecules (response, p. 7).

However, applicants' argument is misplaced because the core referred to by Uhrich at p. 34, lines 21-22 is not the same “core” that links the molecules of Tian together, which is what applicants are referring to in their argument. What Uhrich actually states at p. 34, lines 21-22 is:

“The PEG arms of the polymers of the present invention thus form a hydrophilic shell that solubilizes the polymer in water, while the core forms a hydrophobic microenvironment that encapsulates small hydrophobic molecules.”

Thus, in context, it is clear that Uhrich indicates that the core is everything but the PEG chains. In fact, this exact arrangement is directly taught by Tian (see Scheme I, where the PEG chains form a hydrophilic external shell and the rest of Tian's molecule forms a hydrophobic microenvironment that encapsulates the drug), further illustrating the functional similarities between the molecules of both Tian and Uhrich.”

Applicants believe the Examiner's discussion misses the main point. At the center of the macromolecules disclosed in Uhrich is a polyol or polyacid core. For example, in Claim 1, R1 is a “core comprising a polyol or polyacid”. This core clearly provides a covalent linking of the component molecules including, for example, the molecules of Tian. Thus, the components of the Uhrich macromolecule are held in a conformation that is clearly different than the conformation shown in Tian, Scheme 1. This conformational difference, along with the disclosure of Uhrich that these ASM molecules do not aggregate with each other, clearly refutes the Examiner's assertion that Tian and Uhrich disclose molecules with “functional similarities.”

Finally, the Examiner states:

“Applicants argue that the requirement to demonstrate the functional part of the molecule is the small polyfunctional core is arbitrary, and that applicants only need to show why the combination of Uhrich and Tian is improper (response, p. 8).

Applicants only need to demonstrate that the function of the small polyfunctional core (the core in Uhrich that links the intermediate molecules of Tian together) outweighs that of the rest of the molecule if they wish their previous arguments to be persuasive. It is not a requirement. However, it is not arbitrary because, based on the teachings of Tian and Uhrich (see above), applicants' arguments are not persuasive in the absence of such evidence. As to applicants' burden to show that the combination of Tian and Uhrich is improper, the examiner agrees that if applicants were to show that this combination of references was improper, the rejections should be withdrawn. However, applicants have not shown why the combination of Tian and Uhrich is improper. Thus, the rejections of record are maintained.”

In response, Applicants believe that they have already shown the combination of references is improper for the reasons stated above. Second, the Examiner has picked an arbitrary feature of the molecule disclosed by Uhrich. As Applicants have pointed out, the core molecule Uhrich constrains the interaction of the molecules of Tian. The molecules disclosed Tian, on the other hand, are free to aggregate with or disaggregate from each other (See Tian, Scheme 1). Finally, the disclosure of Uhrich provides that the “core” provides a thermodynamic stability to the “unimolecular micelle”. Therefore, the combination of Tian and Uhrich remains improper and the burden has not shifted to the Applicants to refute rejection with objective evidence.

It is submitted that the combination of Tian with Uhrich remains improper for sustaining the rejection. Accordingly, reconsideration and withdrawal of the rejection are requested.


Applicant : Kathryn E. Uhrich et al.
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CONCLUSION

The Examiner is invited to contact Applicant's Representative at the below-listed telephone number if there are any questions regarding this Response or if prosecution of this application may be assisted thereby. If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 50-3503. If any extensions of time are needed for timely acceptance of papers, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extension fees to Deposit Account 50-3503.

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